

IN THE SPECIFICATION:

Please amend the specification as follows:

At page 1, after the title, please amend the specification to insert the priority application information as follows:

--This application is a U.S. national phase of International application no. PCT/DE2004/002503, filed November 12, 2004, and claims the benefit of priority of German application no. 103 53 175.0, filed November 14, 2003.--

At page 8, paragraph 3, to page 9, first paragraph, please amend the specification to insert the underlined amino acid positions of the referenced sequences, and delete the strikethrough text, as follows:

--The complementarity-determining regions (CDRs) of the polypeptide sequence includes the amino acid sequence that is essentially identical to the amino acid sequence Ser-Gly-Asp-Lys-Leu-Gly-Asp-Lys-Tyr-Ala-Cys (CDR1), amino acids 23-33 of SEQ ID NO:1, Gln-Asp-Ser-Lys-Arg-Pro-Ser (CDR2), amino acids 49-55 of SEQ ID NO:1, and Gln-Ala-Trp-Asp-Ser-Ser-Ile-Val-Val (CDR3), amino acids 88-96 of SEQ ID NO:1 of the variable region of the light chain (VL); see also Figure 2 Page 2 of the Listing.

The complementarity-determining regions (CDRs) of the peptide sequence include amino acid sequences that are essentially identical to Ser-Tyr-Ala-Met-His (CDR1), amino acids 31-35 of SEQ ID NO:3, Val-Ile-Ser-Tyr-Asp-Gly-Ser-Asn-Lys-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly (CDR2), amino acids 50-66 of SEQ ID NO:3, and Asp-Arg-Leu-Ala-Val-Ala-Gly-Lys-Thr-Phe-Asp-Tyr (CDR3), amino acids 99-110 of SEQ ID NO:3 of the variable region of the light chain (V_H); see also Figure 4 Page 4 of the Listing.--

At pages 19-22, please amend the specification to insert the underlined text and delete the strikethrough text to correct the numbering of the Figures as follows:

--Explanation of figures

Sequence listing

Figure 1 Page 1 of the Listing shows the amino acid sequences (SEQ ID NO:1) of the variable region of the light chain (V_L).

Figure 2 Page 2 of the Listing shows the nucleotide acid sequences (SEQ ID NO:2) of the variable region of the light chain (V_L). The complementarity-determining regions (CDRs) are indicated by horizontal lines and are substantially identical to nucleotides 67-99 (CDR1), 145-165 (CDR2) and 262-288 (CDR3) of SEQ ID NO:2.

Figure 3 Page 3 of the Listing shows the amino acid sequences (SEQ ID NO:3) of the variable region of the heavy chain (V_H).

~~Figure 4~~ Page 4 of the Listing shows the nucleotide acid sequence (SEQ ID NO:4) of the variable region of the heavy chain (V_H). The complementarity-determining regions (CDRs) are indicated by horizontal lines and are substantially identical to nucleotides 91-105 (CDR1), 148-198 (CDR2) and 295-330 (CDR3) of SEQ ID NO:4.

Cell-biological experiments

DESCRIPTION OF FIGURES

The figures explained below are not intended to restrict the invention, but only to explain it and prove its feasibility with reference to examples.

~~Figure 5~~ Figure 1 shows the measurement of oxLDL in dependence on the incubation time with a copper sulphate solution. In the experiment, LDL (Sigma, Taufkirchen, Germany) was oxidized for 3 and 15 h respectively by incubation with 20 µM CuSO₄. The amount of oxidized LDL was determined with the Mercodia Oxidized LDL ELISA, according to the instructions for use. It can be clearly seen that the amount of oxidized LDL increases with increasing incubation time, with each LDL fraction that was not treated with copper ions being already partly present in oxidized form. After 15 hours' incubation, the proportion of oxidized LDL has approximately doubled.

~~Figure 6~~ Figure 2 shows the proof of binding of SAM-6 to oxLDL. To prove binding of SAM-6 to oxLDL by means of the ELISA binding assay, the ELISA plate was precoated with LDL fractions oxidized to different degrees before the primary antibody SAM-6 and the secondary antibody anti-human IgM, required for detection purposes, were added. The result shows that the more LDL that is present in its oxidized form, the more strongly the antibody SAM-6 according to the invention binds.

~~Figure 7~~ Figure 3 shows the result of an FACS analysis. The cells used for this purpose are of the mouse macrophage cell line P388D1(IL-1) (DSMZ Accession No. ACC 288). Figure [[7A]] 3A shows the binding of LDL to macrophages. Figure [[7B]] 3B proves that the human monoclonal antibody SAM-6, too, binds to macrophages. The proof of binding of a control IgM to macrophages in Figure [[7C]] 3C demonstrates that the macrophages possess µ receptors. The rightward shift of the signal in Figure [[7D]] 3D demonstrates that simultaneous incubation of LDL and SAM-6 effect a multiple binding of SAM-6 to the cells.

~~Figures 8 and 9~~ Figure 4 and 5 show the result of the Sudan III staining, for which the cells of the mouse macrophage cell line P388D1(IL-1) were used. ~~Figure 8~~ Figure 4 shows cells that were incubated for 48 h with either SAM-6 or an IgM control antibody and subsequently subjected to Sudan III staining. The cells incubated with the antibody SAM-6 show, by their red coloration, distinct deposition of neutral fats. The cells incubated with the control antibody by contrast show no changes.

For the stains shown in Figure 9 Figure 5, the macrophages were cultivated for 24 h both with and without FCS supplement. Then, for a further 24 h, either only LDL, or only SAM-6, or LDL and SAM-6 together were respectively added. Subsequently staining with Sudan III was carried out. The left figure column with the Figures 9A, 9C and 9E 5A, 5C and 5E show cells that were cultivated without supplementation of FCS. The right image column with the Figures 9B, 9D and 9F 5B, 5D and 5F show cells that were cultivated with supplementation of FCS.

Figures 9A and 9B 5A and 5B demonstrate that both macrophages that were cultivated without FCS and macrophages that have grown in the presence of FCS show basal deposition of neutral fats. Figure [[9C]] 5C demonstrates that when SAM-6 is supplemented to

macrophages that were cultivated without FCS, no fat deposition is evident. As shown in Figure ~~[[9D]]~~ 5D, on the other hand, a reinforced lipid accumulation is observed in macrophages that were cultivated with FCS and subsequently had SAM-6 added to them. Figures ~~9E and 9F~~ 5E and 5F demonstrate that, with a co-incubation of SAM-6 and LDL, the intracellular lipid accumulation increases substantially both in macrophages that were cultivated with FCS and in those that have grown without the addition of FCS.

~~Figure 10~~ Figure 6 shows the effect of the antibody SAM-6 on LDL values *in vivo*. In the experiment, 1 mg of purified SAM-6 antibodies and, in the control experiment, 1 mg of human Chrompure IgM (isotype control) were injected into the mice intraperitoneally. The LDL concentration in the blood was measured after 24 and 48 h. After 24 and 48 hours, a clear reduction of serum LDL can be observed in the mice treated with SAM-6.

The measurement of LDL in the blood serum was carried out automatically with the MODULAR D P800 instrument (Roche), the plotted values being obtained as a result of the "LDL Cholesterol Direct" diagnostic kit (Roche Diagnostics).

~~Figure 11~~ Figure 7 also demonstrates the *in vivo* effect of SAM-6.10, an indirect method according to the Friedewald formula being used to calculate the values. Here, the amount of LDL is calculated from the difference between total cholesterol, HDL and triglycerides. According to this manner of evaluating the experiment, the reduction of the concentration of LDL in the serum after SAM 6.10 treatment is even greater. However, this indirect measurement method must be regarded as less accurate in comparison to the method used in ~~Figure 10~~ Figure 6.--